

REMARKS

This Amendment responds to the Office Action mailed February 5, 2009. With this amendment, Applicant amends claims 5-8, and adds claims 9-12. Applicant notes that the Office has deemed claims 1-4 directed to non-elected subject matter and therefore withdrawn these claims from consideration. Thus, claims 5-12 are currently pending and under consideration.

This amendment adds no new matter and finds support throughout the specification and claims as filed, including, e.g., previously presented claims 1-8, as well as at pages 12-15, paragraphs [0022]-[0024].

Information Disclosure Statement

Applicant thanks the Examiner for consideration of the Information Disclosure Statements filed on November 30, 2006 and July 28, 2008. Applicant notes that the Examiner has initialed the English language abstracts and/or an English language patent family member for the Japanese documents listed in the PTO-1449, therefore, no further consideration is needed for the Japanese language documents.

Claim Rejections – 35 U.S.C. § 112, First Paragraph - Enablement

The Action rejects claims 5-8 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement.

Applicant respectfully notes that, without expressing agreement with or acquiescence to the rejections, claims 5-8 have been amended. Claim 5 has been amended to delete references to “prevention.” Applicant notes that claims 6-9 depend directly or indirectly from the amended

claim, and therefore, benefit from the amendment. This amendment finds support in the specification, for example, at page 4.

Applicant further notes that the Action states that Applicant “is enabled for treatment of vasospasm accompanying a bypass operation” (Office Action page 2, last paragraph). Applicant respectfully submits that the specification enables a person skilled in the art to practice the invention as presently claimed.

Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Claim Rejections – 35 U.S.C. § 102(b)

The Office Action rejects claims 5-8 as being anticipated by Batchelor et al. (British Journal of Pharmacology, 2001, vol. 132, pages 302-308). In particular, the Office Action asserts that “the claimed method never requires administering to a patient that has vasospasm or a bypass operation, the only requirement is that the person be ‘in need’ of the fasudil.” (Office Action at page 5, first paragraph.)

In response, Applicant respectfully submits that without expressing agreement with or acquiescence to the rejections, claims 5-8 have been amended. For example, claim 5 has been amended to recite that the administration is to a “patient who had been subjected to off pump beating coronary artery bypass grafting, wherein the vasospasm is the one that does not respond to a calcium antagonist and/or a nitro-compound.” Applicant notes that claims 6-9 depend directly from the amended claim 5, and therefore, benefit from the amendment. These amendments find support in the specification, at for example, in Examples on pages 12-15,

paragraphs [0022] – [0024]. Applicant submits that at least these elements are not disclosed in Batchelor et al., and thus, claims 5-8 are not anticipated by Batchelor et al.

Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 102(b).

Claim Rejections – 35 U.S.C. § 102(a)

The Office Action rejects claims 5-8 as being anticipated by Inokuchi et al. (Journal of Cardiovascular Pharmacology, 2004, Vol. 44, No. 3), under 35 U.S.C. § 102(e).

Initially, Applicant respectfully notes that the Action incorrectly refers to this rejection as a 102(e) rejection, when a rejection under 35 U.S.C. § 102(a) was apparently intended.

In response to the rejection under 35 U.S.C. § 102(a), Applicant submits herewith a verified English translation of the priority document, JP 2004/020882, which has a filing date of January 29, 2004; thereby perfecting foreign priority. Applicant respectfully requests that the Examiner consider the translated priority document and determine its effect on the rejection under 35 U.S.C. § 102(a).

Claim Rejections – 35 U.S.C. § 103

The Office Action rejects claims 5-8 as being unpatentable over Batchelor et al. in view of Satoh et al. (Japanese Journal of Pharmacology, 2001, Vol. 87) under 35 U.S.C. § 103. In particular, with regard to claim 5, the Action states that Batchelor et al. “teaches treatment of coronary artery bypass surgery with HA 1077, also known as fasudil (on page 304, column 1, third paragraph) . . . [and] vasospasms are a problem in coronary artery surgery (abstract)” (Office Action page 7, last paragraph). The Action states that Satoh et al. “teaches that both fasudil and hydroxyfasudil . . . protect the heart against vasopressin and inhibit Rho-kinase

(abstract) . . . [and] that fasudil may have beneficial effects in treating coronary vasospasm (page 34, column 2, paragraph 2).” (Office Action page 7, last paragraph).

Applicant respectfully submits that claim 5 has been amended to delete reference to “prevention” and to recite that the administration is to a “patient who had been subjected to off pump beating coronary artery bypass grafting, wherein the vasospasm is the one that does not respond to a calcium antagonist and/or a nitro-compound.” Applicant notes that claims 6-9 depend directly or indirectly from the amended claim, and therefore, benefit from the amendment. All of these amendments find support in the specification, at for example, pages 4 and 12-15.

Applicant respectfully disagrees with the Action’s determination regarding obviousness. Applicant submits that a *prima facie* case for obviousness has not been established, particularly because there is no showing that (1) the combination of references teaches or suggests every element of the claims; (2) a reason to modify the reference teachings to arrive at the claimed invention; and (3) a reasonable expectation that the guided result will be successful. Indeed, Applicant submits that the Office has not shown those elements because those elements are not present.

The Cited Art Fails to Teach or Suggest the Elements of the Claims

Applicant submits that Batchelor et al. and Satoh et al. do not teach a method for treatment for vasospasm resulting from a bypass operation, which comprises administering after the bypass operation, an effective amount of an agent to a patient who had been subjected to off pump beating coronary artery bypass grafting, wherein the vasospasm is the one that does not respond to a calcium antagonist and/or a nitro-compound, using fasudil.

With respect to Batchelor et al., Applicant notes that Batchelor et al. discuss vasospasms occurring after coronary artery surgery. Batchelor et al. also study the effect rho-kinase inhibitors have on left internal mammary arteries that could be used for coronary artery surgery. However, Batchelor et al. focuses on the prevention of the vasospasm. (Page 302, abstract). As stated in the last sentence of the abstract, Batchelor et al. notes that “[r]ho-kinase inhibitors may have an important role in *preventing* vasospasm in arterial grafts used for coronary artery surgery.” (Emphasis added.) Batchelor et al. do not teach or suggest treating post bypass coronary artery surgery vasospasms.

Similarly, Satoh et al. teach preventing, but not treating, coronary artery vasospasm. The experiments performed in Satoh et al. show “pretreatment” of the animals subjected to testing, suggesting that any effect observed is more accurately characterized as “prevention.” Thus, Applicant respectfully submits that Satoh et al. does not teach or suggest treating post bypass coronary artery surgery vasospasms.

There is No Reason to Modify the Reference Teachings

Applicant also respectfully notes that there is no reason to modify the reference teachings to arrive at the presently claimed invention. As noted above, the cited art teaches that fasudil and hydroxyfasudil are useful in preventing coronary artery vasospasm; thus, these documents teach and suggest administration of the agents prior to the occurrence of the vasospasm. However, neither document teaches or suggests administering the agent during or after a procedure that produces the vasospasm.

There Would Be No Expectation of Success to Modify the Reference Teachings

Applicant further submits that there would be no expectation of success if the reference teachings were modified to arrive at the presently claimed invention. As emphasized above, the

cited art tested the effects of fasudil and hydroxyfasudil in preventing coronary artery vasospasm. The conclusions drawn by these authors should not be extended to indications that were not tested.

Applicant respectfully notes that the field of treating coronary artery vasospasms is highly unpredictable. There are a variety of types of vasospasms, depending on the tissues, organs, and conditions to which they are related. As a result of this variety, it is difficult to precisely predict whether an agent will exhibit preventative and/or treating effects without actual experimental results.

As noted in the Background section of the specification, an arterial bypass operation is performed when occlusion or stenosis of an artery has occurred. Upon the arterial bypass operation, arterial spasm may occur during or after a coronary artery bypass grafting. The arterial spasm is characterized by being more intense and persistent than the arterial spasm that occurs during a nonoperative period. Further, the arterial spasm does not respond well to nitro-compounds or calcium antagonists, which have been administered *after* the occurrence of the arterial spasm, resulting in a large clinical problem in the bypass operation (Hiroshi Hayafuji, "Separate volume, Nippon Rinsho, Series: Syndromes in separate regions No. 12, Syndromes in Circulatory Organs I, including other Circulatory Diseases," First Edition, Nippon Rinsho Corporation, August 30, 1996, p.667-671).

As further evidence of this phenomenon, Applicant notes that in Example 1 of the present specification, isosorbide dinitrate (a "nitro-compound"), diltiazem (a calcium channel blocker, or "calcium antagonist"), and nicorandil (nitric oxide donor) had no effect on coronary artery vasospasm when administered, during and after the operation, to a patient who had been subjected to off pump beating coronary artery bypass grafting. Similar results are described in

Examples 2 and 3. Applicant respectfully notes that these compounds are examples of compounds described in Batchelor et al. as having been used to prevent arterial graft spasm, or “antispasmodics.” (Page 302, right column, second paragraph.)

Also as noted in the Background of the specification, a compound represented by the general formula (I) (such as fasudil or hydroxyfasudil) has an inhibitory activity against kinases such as Rho kinase, myosin light chain kinase or protein kinase C, and represents a relaxing effect on vascular smooth muscles, an increasing effect on blood flow, a reducing effect on blood pressure, a protecting effect on a brain or heart, or the like. Thus, it is known that the compound represented by the general formula (I) serves as an effective substance for a vasodilating agent (especially, for a therapeutic agent for angina pectoris), a therapeutic agent for hypertension, a protecting agent for a brain or heart, a therapeutic agent for arteriosclerosis (references omitted).

However, as noted in the Background section, the arterial spasm during the bypass operation is refractory to treatment with common vasodilating agents, including the nitro-compounds and the calcium antagonists, and therefore the vasodilating agent is not necessarily effective in the prevention of and treatment for the vasospasm accompanying the bypass operation.

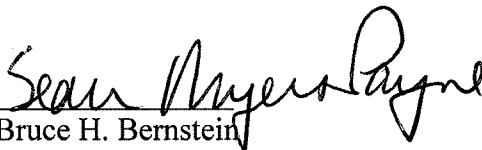
In view of the foregoing remarks, Applicant respectfully submits that a *prima facie* case of obviousness is not established by the cited art. However, if the Office maintains the rejection and believes a *prima facie* case has been established, Applicant wishes to point out that Examples 1, 2, and 3 demonstrate that when administered for the specific (claimed) indication of treating vasospasm in a patient who had been subjected to off pump beating coronary artery bypass grafting, the spasm was completely abolished by the treatment and follow up, which is an unexpectedly good result.

In view of the foregoing, Applicant respectfully requests withdrawal of the outstanding rejections for obviousness.

CONCLUSION

In view of the foregoing, Applicant respectfully requests the Examiner to reconsider and withdraw the rejections of record, and allow all the pending claims.

Respectfully Submitted,
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